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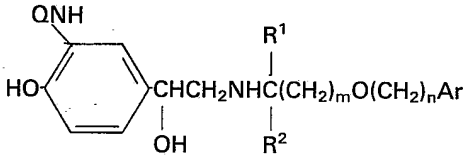
(54) Aminophenol compounds

(57) Compounds of the formula (I)



(I)

wherein
m is from 2 to 8 and
n is from 1 to 7, the total or m+n being 4 to 12;
Ar represents an optionally substituted phenyl group
R^1 and R^2 each represents a hydrogen atom or a C_{1-3} alkyl group the sum total of carbon atoms in R^1 and R^2 being not more than 4;
Q represents a group R^3CO-, R^3NHCO-, $R^3R^4NSO_2-$ or R^5SO_2-, where R^3 and R^4 each represents a hydrogen atom or a C_{1-3} alkyl group and R^5 represents a C_{1-4} alkyl group; and physiologically acceptable salts and solvates thereof, have a selective *stimulant action at B_2– adrenoreceptors* and are useful, in particular, in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

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Formulae in the printed specification were reproduced from drawings submitted after the date of filing, in accordance with Rule 20(14) of the Patents Rules 1982.

This print embodies corrections made under Section 117(1) of the Patents Act 1977.

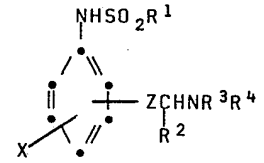
SPECIFICATION

Aminophenol compounds

This invention relates to aminophenol derivatives having a stimulant action at β_2-adrenoreceptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

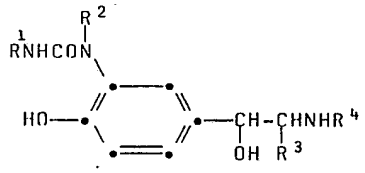
Aminophenol derivatives possessing a sulphonamido or ureido substituent n the phenol ring have previously been described as bronchodilators having stimulant activity at β-adrenoreceptors.

Thus British Patent Specification No. 993584 describes compounds of the general structure

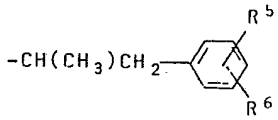


in which R^1 represents lower alkyl, phenyl or tolyl; X represents inter alia hydroxy; Z represents inter alia $-CH(OH)-$; R^2 and R^3 each represent inter alia hydrogen; and R^4 represents hydrogen, lower alkyl, or aralkyl or aryloxyalkyl in which the aryl ring may optionally be substituted by hydroxy, methoxy or methylenedioxy.

British Patent Specification No. 1286225 describes compounds of the general structure.



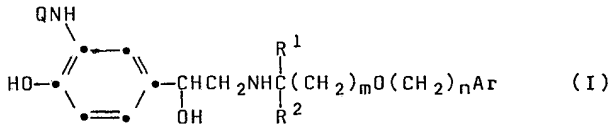
in which R^1 represents hydrogen, C_{1-5} alkyl, phenyl, dimethylaminoethyl or dimethylaminopropyl; R^2 and R^3 each represent inter alia hydrogen; and R^4 represents C_{3-5} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkylmethyl or the group



where R^5 and R^6 each represent hydroxy or methoxy.

We have now found a novel group of aminophenol derivatives, which differ structurally from those described in British Patent Specifications Nos. 993584 and 1286225, and which have a desirable and useful profile of activity.

Thus, the present invention provides compounds of the general formula (I)



(I)

wherein

m is an integer from 2 to 8 and

n is an integer from 1 to 7 with the proviso that the sum total of m+n is 4 to 12;

Ar represents a phenyl group optionally substituted by one or more substituents selected from halogen atoms,

C_{1-6}alkyl or C_{1-6}alkoxy groups, or an alkylenedioxy group of formula $-O(CH_2)_pO-$, where p represents 1 or 2;

R^1 and R^2 each represents a hydrogen atom or a C_{1-3} alkyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 4;

Q represents a group R^3CO-, R^3NHCO-, $R^3R^4NSO_2-$ or R^5SO_2-, where R^3 and R^4 each represents a hydrogen atom or a C_{1-3} alkyl group and R^5 represents a C_{1-4} alkyl group; and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

It will be appreciated that the compounds of general formula (I) possess one or two asymmetric carbon atoms, namely the carbon atom of the

group and, when R^1 and R^2 are different groups, the carbon atom to which these are attached.

The compounds according to the invention thus include all enantiomers, diastereoisomers and mixtures thereof, including racemates. Compounds in which the carbon atom in the

group is in the R configuration are preferred.

In one aspect, the invention provides compounds of formula (I) in which m, n, R^1 and R^2 are as defined above, Ar represents a phenyl group optionally substituted by one or two substituents selected from halogen atoms, C_{1-3} alkyl or C_{1-3} alkoxy groups, or an alkylenedioxy group of formula $-O(CH_2)_pO-$ where p is 1 or 2, and Q represents the group R^3CO-, R^3NHCO- or R^5SO_2- where R^3 and R^4 are as defined in formula (I), and R^5 represents a C_{1-3} alkyl group.

In the general formula (I), the chain $-(CH_2)_m-$ may be for example $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$ or $-(CH_2)_7-$, and the chain $-(CH_2)_n-$ may be for example $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_6-$.

Preferably, the total number of carbon atoms in the chains $-(CH_2)_m-$ and $-(CH_2)_n-$ is 6 to 12 inclusive and may be for example 7, 8, 9 or 10. Compounds wherein the sum total of m + n is 7, 8 or 9 are particularly preferred.

Preferred compounds of general formula (I) are those wherein m is 2 or 3 and n is 6, or m is 4 and n is 3, 4 or 5, or m is 5 and n is 2, 3 or 4. Most preferably m is 5 and n is 4.

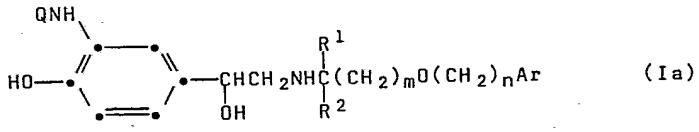
In the compounds of formula (I) R^1 and R^2 may each be, for example, methyl, ethyl, propyl or isopropyl groups except that if one of R^1 and R^2 is a propyl or isopropyl group, the other is a hydrogen atom or a methyl group. Thus for example R^1 may be a hydrogen atom or a methyl, ethyl or propyl group. R^2 may be, for example, a hydrogen atom or a methyl group. R^1 and R^2 are each preferably a hydrogen atom or a methyl group.

A preferred group of compounds is that wherein R^1 and R^2 are both hydrogen atoms, or R^1 is a hydrogen atom and R^2 is a C_{1-3} alkyl group, particularly a methyl group.

In the group Q, R^3 and R^4 may each be for example, a hydrogen atom or a methyl, ethyl, propyl or isopropyl group, and R^5 may be for example a methyl, ethyl, propyl, isopropyl or butyl group. Preferably R^3 represents hydrogen or methyl, R^4 represents hydrogen or methyl, and R^5 represents C_{1-3} alkyl. Preferred meanings for the group Q are HCO–, CH_3CO-, NH_2CO-, $(CH_3)_2NSO_2-$, and R^5SO_2 where R^5 is C_{1-3} alkyl, more particularly methyl or n-propyl. A preferred group of compounds is that wherein Q is the group HCO,– NH_2CO- or, more preferably, CH_3SO_2-.

Examples of the optional substituents which may be present on the phenyl group represented by Ar include bromine, iodine or, in particular, chlorine or fluorine atoms, or a C_{1-3} alkyl group (e.g. methyl or ethyl), or a C_{1-3} alkoxy group (e.g. methoxy or ethyoxy). The phenyl group represented by Ar may for example contain one or two substituents, which may be present at the 2-, 3-, 4-, 5- or 6-positions on the phenyl ring. Ar is preferably a phenyl group optionally substituted by one substituent, particularly a methyl group or a fluorine atom. More preferably Ar represents an unsubstituted phenyl group.

A preferred group of compounds are those of the formula (Ia)



(Ia)

wherein

m is an integer from 2 to 5; n is an integer from 2 to 6, and the sum total of m+n is 7, 8 or 9;
R^1 represents hydrogen and R^2 represents a hydrogen atom or a methyl group;
Ar represents a phenyl group optionally substituted by a methyl group or a fluorine atom; and
Q represents HCO–, CH_3CO-, NH_2CO-, $(CH_3)_2NSO_2-$ or R^5SO_2- where R^5 is C_{1-3} alkyl; and physiologically acceptable salts and solvates thereof.

A particularly preferred group of compounds of formula (Ia) is that wherein m is 5 and n is 4.

Another particularly preferred group of compounds of formula (Ia) is that wherein Q is R^5SO_2- and R^5 is a methyl group.

In a further particularly preferred group of compounds of formula (Ia), Ar is a phenyl group substituted by a fluorine atom or, more preferably, an unsubstituted phenyl group.

Particularly important compounds of the invention are:
N-[2-hydroxy-5-[1-hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenyl]methanesulphonamide;
N-[2-hydroxy-5-[1-hydroxy-2-[[6-[4-(4-fluorophenyl)butoxy]hexyl]amino]ethyl]phenyl]methanesulphonamide;
N[2-hydroxy-5-[1-hydroxy-2-[[1-methyl-6-(2-phenylethoxy)hexyl]amino]ethyl]phenyl]methanesulphonamide;

N-[2-hydroxy-5-[1-hydroxy-2-[[6-(3-phenylpropoxy)hexyl]amino]ethyl]phenyl]formamide;
N-[2-hydroxy-5-[1-hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenyl]urea;
N-[2-hydroxy-5-[1-hydroxy-2-[[3-[(6-phenylhexyl)oxy]propyl]amino]ethyl]phenyl]methanesulphonamide;
N-[2-hydroxy-5-[1-hydroxy-2-[[6-(3-phenylpropoxy)hexyl]amino]ethyl]phenyl]urea;
N-[2-hydroxy-5-[1-hydroxy-2-[[6-(3-phenylpropoxy)hexyl]amino]ethyl]phenyl]methanesulphonamide;
N-[2-hydroxy-5-[1-hydroxy-2-[[6-[4-(4-methylphenyl)butoxy]hexyl]amino]ethyl]phenyl]methane-sulphonamide;
and the physiologically acceptable salts and solvates thereof.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides, sulphates, phosphates, maleates, tartrates, citrates, benzoates, 4-methoxy-benzoates, 2- or 4-hydroxybenzoates, 4-chlorobenzoates, p-toluenesulphonates, methanesulphonates, sulphamates, ascorbates, salicylates, acetates, fumarates, succinates, lactates, glutarates, gluconates, tricarballylates, hydroxy-naphthalenecarobylates e.g. 1-hydroxy- or 3-hydroxy-2-naphthalene-carboxylates, or oleates. The compounds may also form salts with suitable bases. Examples of such salts are alkali metal (e.g. sodium and potassium), and alkaline earth metal (e.g. calcium or magnesium) salts.

The compounds according to the invention have a selective stimulant action at β_2-adrenoreceptors, which furthermore is of a particularly advantageous profile. The stimulant action was demonstrated in the isolated trachea of the guinea-pig, where compounds were shown to cause relaxation of $PGF_{2\alpha}$—induced contractions. Compounds according to the invention have shown a particularly long duration of action in this test.

The compounds according to the invention may be used in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

The compounds according to the invention may also be used for the treatment of premature labour, depression and congestive heart failure, and are also indicated as useful for the treatment of inflammatory and allergic skin diseases, glaucoma, and in the treatment of conditions in which there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

The invention accordingly further provides compounds of formula (I) and their physiologically acceptable salts and solvates for use in the therapy or prophylaxis of diseases associated with reversible airways obstruction in human or animal subjects.

The compounds according to the invention may be formulated for administration in any convenient way. The invention therefore includes within its scope pharmaceutical compositions comprising at least one compound of formula (I) or a physiologically acceptable salt or solvate thereof formulated for use in human or veterinary medicine. Such compositions may be presented for use with physiologically acceptable carriers or excipients, optionally with supplementary medicinal agents.

The compounds may be formulated in a form suitable for administration by inhalation or insufflation, or for oral, buccal, parenteral, topical (including nasal) or rectal administration. Administration by inhalation or insufflation is preferred.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in for example capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For buccal administration the composition may take the form of tablets, drops or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration. Formulations for injections may be presented in unit dosage form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For topical administration the pharmaceutical composition may take the form of ointments, lotions or creams formulated in a conventional manner, with for example an aqueous or oily base, generally with the addition of suitable thickening agents and/or solvents. For nasal application, the composition may take the form of a spray, formulated for example as an aqueous solution or suspension or as an aerosol with the use of a suitable propellant.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or

retention enemes, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

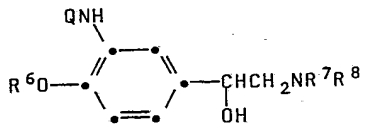
Where pharmaceutical compositions are described above for oral, buccal, rectal or topical administration, these may be presented in a conventional manner associated with controlled release forms.

A proposed daily dosage of active compound for the treatment of man is 0.005mg to 100mg, which may be conveniently administered in one or two doses. The precise dose employed will of course depend on the age and condition of the patient and on the route of administration. Thus a suitable dose for administration by inhalation is 0.005mg to 20mg, for oral administration is 0.02mg to 100mg, and for parenteral administration is 0.01mg to 2mg for administration by injection and 0.01mg to 25mg for administration by infusion.

The compounds according to the invention may be prepared by a number of processes, as described in the following wherein Q, m, n, Ar, R^1 and R^2 are as defined for general formula (I) unless otherwise specified. It will be appreciated that certain of the reactions described below are capable of affecting other groups in the starting material which are desired in the end product; this applies especially in the reduction processes described, particularly where a hydride reducing agent is used and end-products are required in which Q represents the group R^3CO-, and where hydrogen and a metal catalyst are used in the preparation of intermediates containing an ethylene or acetylene linkage. Care must therefore be taken in accordance with conventional practice, either to use reagents which will not affect such groups, or to perform the reaction as part of a sequence which avoids their use when such groups are present in the starting material. In the general processes described below the final step in the reaction may be the removal of a protecting group. Suitable protecting groups and their removal are described in general process (2) below.

According to one general process (1), a compound of general formula (I) may be prepared by alkylation. Conventional alkylation procedures may be used.

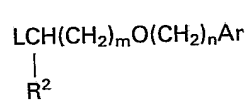
Thus, for example, in one process (a), a compound of general formula (I) in which R^1 is a hydrogen atom may be prepared by alkylation of an amine of general formula (II)



(II)

(wherein each of R^6 and R^7 is a hydrogen atom or a protecting group and R^8 is a hydrogen atom) followed by removal of any protecting group where present.

The alkylation (a) may be effected using an alkylating agent of general formula (III):

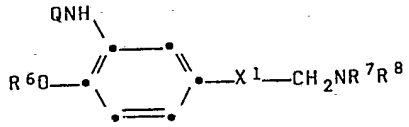


(III)

wherein L represents a leaving group, for example a halogen atom such as chlorine, bromine or iodine, or a hydrocarbylsulphonyloxy group such as methanesulphonyloxy or p-toluenesulphonyloxy.

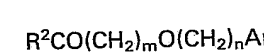
The alkylation is preferably effected in the presence of a suitable acid scavenger, for example, inorganic bases such as sodium or potassium carbonate, organic bases such as triethylamine, diisopropylethylamine or pyridine, or alkylene oxides such as ethylene oxide or propylene oxide. The reaction is conveniently effected in a solvent such as acetonitrile or an ether e.g. tetrahydrofuran or dioxan, a ketone e.g. butanone or methyl isobutyl ketone, a substituted amide e.g. dimethylformamide or a chlorinated hydrocarbon e.g. chloroform, at a temperature between ambient and the reflux temperature of the solvent.

According to another example (b) of an alkylation process, a compound of general formula (I) in which R^1 represents a hydrogen atom may be prepared by alkylation of an amine of general formula (IV):



(IV)

where R^6 and R^7 are as previously defined, R^8 represents a hydrogen atom or a group convertible thereto under the reaction conditions, and X^1 represents $-CH(OH)-$ or $>C=O$ with a compound of general formula (V):



(V)

in the presence of a reducing agent, followed when necessary by removal of any protecting groups.

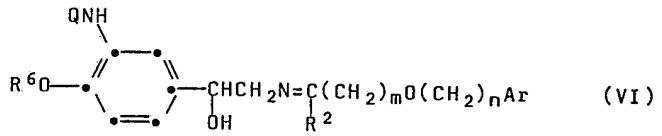
Examples of suitable R^8 groups convertible into a hydrogen atom are arylmethyl groups such as benzyl, α-methylbenzyl and benzhydryl.

Suitable reducing agents include hydrogen in the presence of a catlyst such as platinum, platinum oxide, palladium, palladium oxide, Raney nickel or rhodium, on a support such as charcoal, using an alcohol, e.g. ehtanol of an ester e.g. ethyl acetate or an ether e.g. tetrahydrofuran, or water, as reaction solvent, or a

mixture of solvents, e.g. a mixture of two or more of those just described at normal or elevated temperature and pressure, for example from 20 to 100°C and from 1 to 10 atmospheres.

Alternatively when one or both of R^7 and R^8 are hydrogen atoms, the reducing agent may be a hydride such as diborane or a metal hydride such as sodium borohydride, sodium cyanoborohydride or lithium aluminium hydride. Suitable solvents for the reaction with these reducing agents will depend on the particular hydride used, but will include alcohols such as methanol or ethanol, or ethers such as diethyl ether or *tert*-butyl methyl ether, or tetrahydrofuran.

When a compound of formula (II) where R^7 and R^8 are each hydrogen atoms is used, the intermediate imine of formula (VI) may be formed:



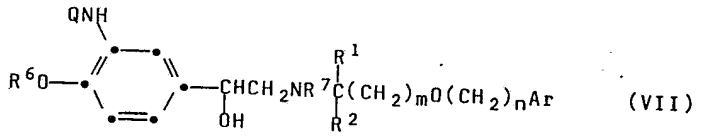
(VI)

(wherein R^6 is as defined for formula (II)).

Reduction of the imine using the conditions described above, followed, where necessary, by removal of any protecting groups, gives a compound of general formula (I).

Where it is desired to use a protected intermediate of general formula (II) or (IV) it is particularly convenient to use hydrogen and a catalyst as described above with protecting groups R^6 and R^7 which are capable of being converted to a hydrogen atom under these reducing conditions, thus avoiding the need for a separate deprotection step. Suitable protecting groups of this type include arylmethyl groups such as benzyl, benzhydryl and α-methylbenzyl.

In another general process (2), a compound of general formula (I) may be obtained by deprotection of a protected intermediate of general formula (VII):



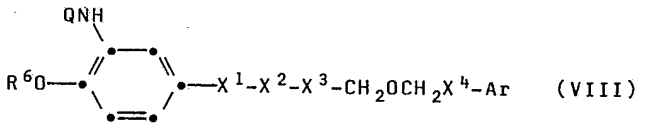
(VII)

(wherein R^6 and R^7 are as previously defined except that at least one of R^6 and R^7 is a protecting group).

The protecting group may be any conventional protecting group, for example as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973). Examples of suitable hydroxyl protecting groups represented by R^6 are aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl and tetrahydropyranyl. Examples of suitable amino protecting groups represented by R^7 are aralkyl groups such as benzyl, α-methylbenzyl, diphenylmethyl or triphenylmethyl and acyl groups such as trichloroacetyl or trifluoroacetyl.

The deprotection to yield a compound of general formula (I) may be effected using conventional techniques. Thus for example, when R^6 and/or R^7 is an aralkyl group this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal). When R^6 is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by R^7 may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroacetyl may be removed by reduction with, for example, zinc and acetic acid. The choice of acyl group R^7 and its method of removal will however depend on the nature of the group Q.

In another general process (3), a compound of general formula (I) may be prepared by reduction. Thus, for example, a compound of general formula (I) may be prepared by reducing an intermediate of general formula (VIII):



(VIII)

(wherein R^6 is as defined for general formula (II) and at least one of X^1, X^2, X^3 and X^4 represents a reducible group and the other(s) take the appropriate meaning as follows, which is X^1 is $-CH(OH)-$, X^2 is $-CH_2NR^7-$, X^3 is $-CR^1R^2(CH_2)_{m-1}-$ and X^4 is $-(CH_2)_{n-1}-$ followed where necessary by removal of any protecting groups.

Suitable reducible groups include those wherein X^1 is a group $>C=O$, X^2 is a group $-CH_2NY-$ (wherein Y represents a group convertible to hydrogen by catalytic hydrogenation, for example an arylmethyl group such as benzyl, benzhydryl or α-methylbenzyl), or an imine ($-CH=N-$) group or a group $-CONH-$, X^3 is a group $-CO(CH_2)_{m-1}-$ or a group $-CR^1R^2X^5-$ where X^5 is C_{2-7} alkenylene or C_{2-7} alkynylene, or $-X^2-X^3-$ is a group $-CH_2N=CR^2(CH_2)_{m-1}-$, or X^4 is C_{2-6} alkenylene or C_{2-6} alkynylene. In one convenient aspect of the reduction process, the group R^6 may be a group convertible to hydrogen under the reducing conditions employed and may be for example an arylmethyl group such as benzyl, benzhydryl or α-methylbenzyl.

The reduction may be effected using reducing agents conveniently employed for the reduction of ketones,

imines, amides, protected amine, alkenes and alkynes. Thus, for example, when X^1 in general formula (VIII) represents a $>C=O$ group this may be reduced to a $-CH(OH)-$ group using hydrogen in the presence of a catalyst as previously described for process (1) part (b). Alternatively, the reducing agent may be, for example, a hydride such as diborane or a metal hydride such as lithium aluminium hydride, sodium bis(2-methoxyethoxy) aluminium hydride, sodium borohydride or aluminium hydride. The reaction may be effected in a solvent, where appropriate an alcohol e.g. methanol or ethanol, or an ether such as tetrahydrofuran, or a halogenated hydrocarbon such as dichloromethane.

When X^2 in general formula (VIII) presents a $-CH_2NY-$ group or the group $-CH=N-$, or X^2-X^3 represents $-CH_2N=CR^2(CH_2)_{m-1}-$ this may be reduced to a $-CH_2NH-$ or $-CH_2NHCHR^2(CH_2)_{m-1}-$ group using hydrogen in the presence of a catalyst as previously described for process (1) part (b). Alternatively, when X^2 or $-X^2-X^3$ is the group $-CH=N-$ or $-CH_2N=CR^2(CH_2)_{m-1}-$ this may be reduced to a $-CH_2NH-$ or $CH_2NHCHR^2(CH_2)_{m-1}-$ group using a reducing agent and conditions as just described for the reduction of X^1 when this represents a $>C=O$ group.

When X^2 or X^3 in general formula (VIII) represents a $-CONH-$ or $-CO(CH_2)_{m-1}-$ group this may be reduced to a group $-CH_2NH-$ or $-CH_2(CH_2)_{m-1}-$ using a hydride such as diborane or a complex metal hydride such as lithium aluminium hydride or sodium bis(2-methoxyethoxy)aluminium hydride in a solvent such as ether, e.g. tetrahydrofuran or diethyl ether.

When X^3 in general formula (VIII) represents a group $-CR^1R^2X^5-$ this may be reduced to a group $-CR^1R^2(CH_2)_{m-1}-$ using hydrogen in the presence of a catalyst as previously described for process (1) part (b).

When X^4 is C_{2-6} alkenylene or C_{2-6} alkynylene this may be reduced to $-(CH_2)_{n-1}-$ using hydrogen and a catalyst as just described. In this aspect of the reduction process, suitable starting materials of formula (VIII) include those in which $CR^1R^2X^5$ and/or X^4 each contains one $-C=C-$ or $-C\equiv C-$ linkage. Where both contain unsaturated linkages, these may be the same or different.

Particular examples of the reduction process are those in which a compound of general formula (I) in which $-(CH_2)_m-$ represents $-(CH_2)_5-$ is prepared from a corresponding compound in which $-(CH_2)_m-$ represents $-CH=CH(CH_2)_3-$, $-C\equiv C(CH_2)_3-$, $-(CH_2)_2CH=CHCH_2-$ or $-(CH_2)_2C\equiv CCH_2-$. In further examples a compound of general formula (I) in which $(-CH_2)_n-$ represents $-(CH_2)_4-$ or $-(CH_2)_3-$ may be prepared by reduction of a corresponding compound of general formula (I) in which $-(CH_2)_n-$ represents $-CH_2CH=CH-CH_2-$, $-CH_2C\equiv CCH_2-$, $-CH_2CH_2CH=CH-$, $-CH_2CH_2C\equiv C-$, $-CH_2CH=CH-$ or $-CH_2C\equiv C-$.

In the general processes described above, the compound of formula (I) obtained may be in the form of a salt, conveniently in the form of a physiologically acceptable salt. Where desired, such salts may be converted to the corresponding free acids using conventional methods.

Physiologically acceptable salts of the compounds of general formula (I) may be prepared by reacting a compound of general formula (I) with an appropriate acid or base in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, ethyl acetate or an alcohol, e.g. methanol, ethanol, or iso-propanol.

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of general formula (I), using conventional methods.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained by resolution of a corresponding racemate of a compound of general formula (I) using conventional methods.

Thus, in one example an appropriate optically active acid may be used to form salts with the racemate of a compound of general formula (I). The resulting mixture of isomeric salts may be separated for example by fractional crystallisation, into the diastereoisomeric salts from which the required enantiomer of a compound of general formula (I) may be isolated by conversion into the required free base.

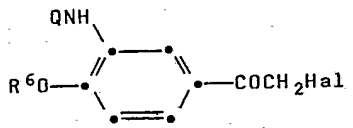
Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

Specific diastereoisomers of a compound of formula (I) may be obtained by conventional methods for example, by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or by conversion of a mixture of isomers of a compound of general formula (I) into appropriate diastereoisomeric derivatives e.g. salts which then can be separated by conventional means e.g. by fractional crystallisation.

Suitable methods for preparing the intermediate compounds used in the above general processes are described below. In the following discussion, Ar, R^1, R^2, R^6, R^7, R^8, Q, X^1, X^2, X^3, X^4, X^5, Y, and L are as defined above except where otherwise indicated. "Hal" represents a halogen atom. Where an intermediate with protected hydroxyl and/or amino group is desired, this may be obtained using conventional protection methods, for example those described by McOmie (see process (2) above).

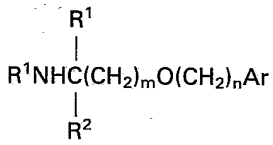
Intermediate compounds of general formula (VIII) for use in general process (3) may be prepared by a number of processes.

Thus for example intermediates of general formula (VIII) in which X^1 is a group $>C=O$ may be prepared from a haloketone of formula (IX):



(IX)

by reaction with an amine of general formula (X):



(X)

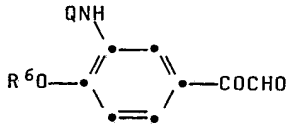
where R^7 is a hydrogen atom or a group convertible thereto by catalytic hydrogenation.

The reaction may be effected in a cold or hot solvent, for example tetrahydrofuran, *tert*-butyl methyl ether, dioxan, chloroform, dimethylformamide, acetonitrile or a ketone such as butanone or methylisobutylketone, or an ester, for example ethyl acetate preferably in the presence of a base such as diisopropylethylamine, sodium carbonate or other acid scavenger such as propylene oxide.

The intermediates of formulae (II) and (IX) are either known compounds or may be prepared according to the methods described by Kaiser *et al* in J. Med. Chem., 1974, *17*, 49, and Larsen *et al* in J. Med. Chem., 1967, *10*, 462.

Intermediates of general formula (VIII) in which X^1 is a group $>C=O$ may be reduced to the corresponding intermediate in which X^1 is a group $-CH(OH)-$ using for example a metal hydride such as sodium borohydride in a solvent e.g. ethanol.

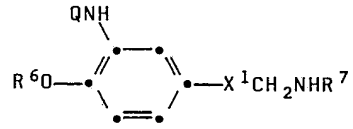
Iminoketones of general formula (VIII) i.e. in which X^2 is a group $-CH=N-$ may be obtained from a phenylglyoxal derivative of formula (XI):



(XI)

by reaction with an amine of formula (X) in which Y represents a hydrogen atom in a solvent such as benzene, tetrahydrofuran or an alcohol e.g. ethanol at temperatures up to the reflux. The phenylglyoxal derivatives of formula (XI) may be obtained from a haloketone of formula (IX) by the action of a dialkylsulphoxide such as dimethylsulphoxide.

Intermediates of general formula (VIII) in which X^3 is a group $-CO(CH_2)_{m-1}-$ may be prepared by acylation of an amine of formula (XII):



(XII)

using an ester or an activated derivative of an acid of formula (XIII):

$$Ar(CH_2)_nO(CH_2)_mCO_2H \qquad \text{(XIII)}$$

Suitable activated derivatives include the acid chloride, an anhydride or imidazolide. The reaction may be optionally carried out in a solvent such as tetrahydrofuran, benzene or chloroform, optionally in the presence of a base such as pyridine or triethylamine. The acids (XIII) may be used directly if a coupling agent such as dicyclohexylcarbodiimide is added.

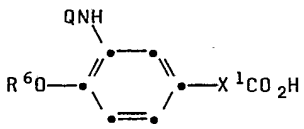
Acids of formula (XIII) may be obtained by treatment of an alcohol of general formula (XIV):

$$Ar(CH_2)_nO(CH_2)_mCH_2OH \qquad \text{(XIV)}$$

with a suitable oxidising agent, for example pyridinium dichromate in a solvent such as dimethylformamide.

Intermediates of formula (VIII) in which $-X^2-X^3-$ represents $-CH_2N=CR^2(CH_2)_{m-1}-$ may be obtained by reaction of an amine of formula (XII) in which R^7 is a hydrogen atom with a compound of formula (V) in a solvent such as acetonitrile.

Intermediates of formula (VIII) in which X^2 is $-CONH-$ may be prepared by reaction of an amine of formula (X) in which R^7 is hydrogen with an acid of formula (XV):



(XV)

in the presence of a coupling agent such as dicyclohexylcarbodiimide. The acids of formula (XV) may be prepared by methods analogous to conventional methods for the preparation of α-keto- and α-hydroxy

carboxylic acids.

Intermediates of formula (VIII) in which X^3 is $-CR^1R^2X^5-$ and/or X^4 is C_{2-6} alkenylene or C_{2-6} alkynylene may be prepared by methods analogous to those described herein for the preperation of compounds of formula (I).

Intermediates of formulae (III), (V), (X) and (XIV) may be prepared as described in U.K. Patent Specification No. 2140800A or by methods analogous to those described therein.

The following examples illustrate the invention. Temperatures are in °C. 'Dried' refers to drying using magnesium sulphate except where otherwise stated. Thin layer chromatography (t.l.c.) was carried out over SiO_2. [C]-column chromotography and [FCS]-flash column chromotography, were both carried out on silica (Merck 9385).

The following abbreviations are used: EA - ethyl acetate; ER - diethyl ether; CX - cyclohexane; ME - methanol; THF - tetrahydrofuran; T - toluene; ET - ethanol; A - 0.88 ammonia solution; DMF - dimethylformamide.

INTERMEDIATE 1

N-[2-(Phenylmethoxy)-5-[[(phenylmethyl)[6-(3-phenylpropoxy)hexyl]amino]acetyl]phenyl]formamide

A solution of *N*-[5-(bromoacetyl)-2-(phenylmethoxy)phenyl]formamide (0.53g), N-[6-(3-phenylpropoxy)hexyl]benzenemethanamine hydrobromide (0.68g) (Compound A) and *N,N*-diisopropylethylamine (0.65g) in dichloromethane (10ml) was kept at 23° for 18h. The mixture was diluted with water (20ml) extracted with ER (30ml) and the organic phase was washed with water (20ml), brine (20ml), dried and evaporated to give an oil. Purification by [FCS] eluting with ER-CX (3:2) afforded the product as a pale yellow oil (0.72g). T.l.c. (ER-CX 3:2) Rf 0.28.

Similarly were prepared:

INTERMEDIATE 2

N-[2-(Phenylmethoxy)-5-[[(phenylmethyl)[6-(3-phenylpropoxy)hexyl]amino]acetyl]phenyl]urea

(1.01g) T.l.c. Et_3N-deactivated silica (EA-CX 4:1) from *N*-[5-(bromoacetyl)-2-(phenylmethoxy)phenyl]urea (0.8g) and Compound A (0.91g).

INTERMEDIATE 3

N-[2-(Phenylmethoxy)-5-[[(phenylmethyl)[6-(3-phenylpropoxy)hexyl]amino]acetyl]phenyl]methane-sulphonamide

(0.5g) T.l.c. (CX-ER 3:2) Rf 0.36 from *N*-[5-(bromoacetyl)-2-(phenylmethoxy)phenyl]methanesulphonamide (0.45g) and Compound A (0.46g.

INTERMEDIATE 4

N-[5-[1-Hydroxy-2-[[6-(4-phenylbutoxy)hexyl](phenylmethyl)amino]ethyl]-2-(phenylmethoxy)phenyl]-methanesulphonamide

To a solution of N-[5-(bromoacetyl)-2-(phenylmethoxy)phenyl]methanesulphonamide (1.9g) and N-[6-(4-phenylbutoxy)hexyl]benzenemethanamine (1.62g) in THF (100ml) stirred under nitrogen was added N,N-diisopropylethylamine (1.23g) and the mixture stirred under nitrogen at room temperature for 40h. The solution was diluted with ER (50ml), filtered and evaporated *in vacuo* to give a brown oil (4.2g) which was dissolved in ME (50ml) and treated with sodium borohydride (0.74g). The mixture was stirred under nitrogen for 1h, diluted with water (150ml) and extracted with ER (2 × 150ml). The organic phase was washed with water (2 × 100ml), dried and evaporated *in vacuo* to give a brown oil. Purification by [FCS] eluting with CX-EA (2:1) gave the *title compound* as a yellow oil (1.92g). T.l.c. (CX-EA 2:1) Rf 0.23.

Found: C,69.8; H,7.8; N,4.2. $C_{39}H_{50}N_2O_5S.O.75H_2O$ requires C,70.0; H,7.7; N,4.2%.

INTERMEDIATE 5

[5-[1-Hydroxy-2-[[6-(4-phenylbutoxy)hexyl](phenylmethyl)amino]ethyl]-2-(phenylmethoxy)phenyl]urea

A solution of N-[5-bromoacetyl)-2-(phenylmethoxy)phenyl]urea (2g) and N-[6-(4-phenylbutoxy)hexyl]-benzenemethanamine (1.87g) in THF (100ml) stirred under nitrogen was treated with N,N-diisopropylethylamine (1.42g). The mixture was stirred at room temperature under nitrogen for 19h, diluted with ER (50ml), filtered and the filtrate was evaporated *in vacuo*. A solution of the resulting orange oil (4.4g) in ME (100ml) was treated with sodium borohydride (1.2g) and stirred under nitrogen for 19h. The mixture was diluted with water (200ml), extracted with ER (2 × 150ml) and the organic phase washed with water (100ml), dried and evaporated *in vacuo* to give an orange oil. Purification by [FCS] eluting with EA-CX (2:1) gave the *title compound* as a yellow oil (1.72g). T.l.c. (EA-ME 3:1) Rf 0.7.

INTERMEDIATE 6

(E)-4-(4-Fluorophenyl)-3-buten-1-ol

n-Butyllithium (1.6M in hexane, 100mℓ) was added dropwise to a stirred suspension of (3-hydroxypropyl)triphenyl-phosphonium bromide (32.1g) in dry THF (200mℓ) cooled to 0°C under nitrogen. A solution of 4-fluorobenzaldehyde (9.93g) in dry THF (100mℓ) was added dropwise and the mixture stirred

under nitrogen at 0°C for 30 min and at room temperature for a further 1.5h. The mixture was carefully diluted with water (25mℓ), the solvent evaporated *in vacuo* at 40° and the residue partitioned between EA (200mℓ) and water (200mℓ). The aqueous phase was re-extracted with EA (200mℓ), the organic phases combined, dried and evaporated *in vacuo* to give a brown oil. Purification by [FCS] eluting with CX-ER (1:1) gave the *title compound* as a colourless oil (6.33g). T.l.c. (CX-ER 1:1) Rf 0.13.

INTERMEDIATE 7

(E)-1-[[4-(6-Bromohexyl)oxy]-2-butenyl]-4-fluorobenzene

A mixture of Intermediate 6 (5.73gm), 1,6-dibromohexane (25.2g), tetrabutylammonium bisulphate (1.5g) and 40% sodium hydroxide solution (45mℓ) was stirred for 18h, diluted with water (200mℓ) and extracted with EA (2×150mℓ). The organic phase was washed with water (100mℓ), brine (100mℓ), dried and evaporated *in vacuo* to give a yellow oil. Purification by [FCS] eluting with CX-EA (10:0 → 9:1) gave a yellow oil (8.49g). T.l.c. (CX-EA 9:1) Rf 0.34.

INTERMEDIATE 8

(E)-N-[2-Hydroxy-5-[1-hydroxy-2-[[6-[[4-(4-fluorophenyl)-3-butenyl]oxy]hexyl]amino]ethyl]phenyl]methanesulphonamide

Intermediate 7 (1.34g) was added to a stirred solution of [5-[(2-amino-1-hydroxyethyl-]-2-hydroxyphenyl]methanesulphonamide (1.50g) and N,N-diisopropylethylamine (0.57g) in DMF (25mℓ) at 70° under nitrogen. The solution was stirred at 70° for 5h, diluted with water (100mℓ) and extracted with EA (2×100mℓ). The organic phase was washed with water (100mℓ), dried (Na_2SO_4) and evaporated *in vacuo* to give a brown oil which was purified by [FCS] on triethylamine deactivated silica (Merck 9385, 100g) eluting with EA-ME (9:1) to give a brown foam (0.5g). Trituration with ER gave the *title compound* as a white solid (0.47g) m.p. 79-80°C (dec.).

INTERMEDIATE 9

N-[5-Acetyl-2-(phenylmethoxy)phenyl]propanesulphonamide

Propanesulphonyl chloride (2.8g) was added to a stirred solution of 1-[3-amino-4-(phenylmethoxy)phenyl]ethanone (3.95g) and triethylamine (3.58g) in dry dichloromethane (80mℓ) at 0°C. The solution was stirred at 0°C for 2h, diluted with ER (200mℓ), washed successively with 2N hydrochloric acid (100mℓ) and 8% sodium bicarbonate solution (100mℓ), dried and evaporated *in vacuo* to give a cream solid. This was slurried in CX to give a solid which was stirred in 1N sodium hydroxide (100mℓ) and filtered off. The filtrate was acidified with 2N hydrochloride acid extracted with EA (2×150mℓ). The combined dried organic extracts were evaporated *in vacuo* to give a cream solid which was recrystallised from EA to give a white solid (3.40g) m.p. 130-130.5°C.

INTERMEDIATE 10

N-[-5-Bromoacetyl-2-(phenylmethoxy)phenyl]propane-sulphonamide

A solution of bromine (1.52g) in chloroform (25mℓ) was added dropwise over 1.5h to a stirred solution of Intermediate 9 (3g) in chloroform (25mℓ) at room temperature. The solution was washed with water (30mℓ), 8% sodium bicarbonate solution (30mℓ) dried (Na_2SO_4) and evaporated *in vacuo* to give a product which was recrystallised from EA affording the *title compound* as a pale orange solid (2.75g) m.p. 99.5-100.5°.

INTERMEDIATE 11

N-[2-(Phenylmethoxy)-5-[2-[[6-(3-phenylpropoxy)hexyl](phenylmethyl)amino]-1-oxoethyl]phenyl]propanesulphonamide

Intermediate 10 (0.65g), *N*-[6-(3-phenylpropoxy)hexyl]-benzenemethanamine (0.5g) and N,N-diisopropylethylamine (0.22g) in DMF (10mℓ) were stirred together under nitrogen for 2.5h. The solution was diluted with water (50mℓ), extracted with EA (2×50mℓ) and the organic phase washed with 2N hydrochloric acid (30mℓ), 8% sodium bicarbonate solution (30mℓ), then dried (Na_2SO_4). Evaporation *in vacuo* gave a yellow oil which was purified by [FCS] eluting with T-EA (9:1) to afford the *title compound* as a colourless oil (77g). T.l.c. (T-EA 9:1) Rf 0.15.

INTERMEDIATE 12

1-[4-[(6-Bromohexyl)oxy]butyl]-4-methylbenzene

A mixture of 4-methylbenzenebutanol (6.5g), 1,6-dibromohexane (24.4g), aqueous sodium hydroxide (50% w/v; 25mℓ), and tetrabutylammonium bisulphate (0.5g) was stirred at room temperature for 20h, diluted with water (50mℓ), and extracted with ER (2×100mℓ). The dried extract was evaporated and the residue was purified by [C] eluting with CX followed by CX-ER (93:7) to give the *title compound* as a colourless oil (9.8g). T.l.c. (CX-ER 9:1) Rf 0.5.

INTERMEDIATE 13

N-[6-[4-(4-Methylphenyl)butoxy]hexyl]benzenemethanamine hydrochloride

Intermediate 12 (5.0g) was added dropwise to benzylamine (25mℓ) at 110°. The solution was heated at 110-120° for 2h, cooled, poured into hdyrochloric acid (2M; 250mℓ), and filtered to give the *title compound* as

a white solid (5.3g) m.p. 119-121°.

INTERMEDIATE 14

3-[(6-Phenylhexyl)oxy]-1-propanol

Sodium (0.95g) was dissolved in warm 1,3-propanediol (9.47g) and then (6-bromohexyl)benzene (10g) was added dropwise. The mixture was stirred under nitrogen at 100° for 3h, poured into water (200mℓ) and 2N hydrochloric acid (30mℓ) and extracted with ER (2×150mℓ), dried and evaporated *in vacuo* to give a yellow oil. Purification by [FCS] eluting with CX-ER (3:1 → 0:1) gave the *title compound* as a colourless oil (5.46g). T.l.c. (CX-ER 3:1) Rf 0.08.

INTERMEDIATE 15

[6-(3-Bromopropoxy)hexyl]benzene

Triphenylphosphine (7.50g) in dry dichloromethane (50mℓ) was added dropwise over 10 min to a stirred solution of intermediate 14 (5.2g) and carbon tetrabromide (9.49g) in dry dichloromethane (90mℓ) at 0°C under nitrogen. The solution was stirred at room temperature for 2h, absorbed onto silica (40g) and purified by [FCS]. Elution with CX-ER (8:1) gave a colourless oil which was distilled to afford the *title compound* as a colourless oil (6.58g). T.l.c. (ER) Rf 0.63.

INTERMEDIATE 16

N,N-Dimethyl-N'-[5-[2-[[6-(4-phenylbutoxy)hexyl](phenylmethyl)amino]-1-oxoethyl]-2-(phenylmethoxy)phenyl]sulphamide

N-[5-Bromoacetyl-2-(phenylmethoxy)phenyl]-*N,N'*-dimethylsulphamide (0.8g), N-[6-(4-phenylbutoxy)hexyl]benzenemethanamine (0.64g) and *N,N*-diisopropylethylamine (0.27g) in DMF (10mℓ) were stirred together at room temperature under nitrogen for 4.5h. The solvent was evaporated *in vacuo* and the residue dissolved in EA (100,ℓ) and washed with water (75mℓ). The aqueous phase was re-extracted with EA (2×50mℓ) and the combined organic phases were dried and evaporated *in vacuo* to give a yellow oil. Purification by [FCS] eluting with T-EA (10:1) gave the *title compound* as a yellow oil (0.66g). T.l.c. (T-EA 5:1) Rf 0.35.

INTERMEDIATE 17

N-[5-(4-Phenylbutoxy)pentyl]benzenemethanamine

[4-[(-Bromopentyl)oxy]butyl]benzene (4.0g) was added dropwise to benzylamine (20ml) at 110°C. The solution was heated at 110-120° for 90 min and cooled. Hydrochloric acid (2M; 125ml) was added and the mixture was extracted with EA (2×100ml). The organic extract was washed with aqueous sodium carbonate (100ml) and brine (100ml), dried, and evporated. The residue was distilled to give the *title compound* as a colourless oil (3.3g) b.p. 190-195°/0.1mmHg. T.l.c. (CX-ER 1:1) Rf 0.25.

EXAMPLE 1

N-[2-Hydroxy-5-[1-hydroxy-2-[[6-(3-phenylpropoxy)hexyl]amino]ethyl]phenyl]formamide

A solution of Intermediate 1 (0.25g) in ethanol (20ml) was hydrogenated at room temperature and atmospheric pressure over 10% palladium on carbon (0.15g) and 10% platinum on carbon (0.15g) catalysts. The mixture was filtered through hyflo and evaporated *in vacuo*. The residue was triturated with ER and cooled to give the product as a white solid (0.092g), m.p. 85-86° (dec.). T.l.c. Et_3N-deactivated silica (EA-ME 7:3) Rf 0.68.

Similarly were prepared:-

EXAMPLE 2

N-[2-Hydroxy-5-[1-hydroxy-2-[[6-(3-phenylpropoxy)hexyl]amino]ethyl]phenyl]urea, m.p. 78-80°. T.l.c. Et_3N-deactivated silica (EA-ME 7:3) Rf 0.62 (0.26g) from Intermediate 2 (0.6g).

EXAMPLE 3

N-[2-Hydroxy-5-[1-hydroxy-2-[[6-(phenylpropoxy)hexyl]amino]ethyl]phenyl]methanesulphonamide, m.p. 130-134° (dec.) T.l.c. Et_3N-deactivated silica (EA-ME 7:3) Rf 0.62 (0.13g) from Intermediate 3 (0.3g).

EXAMPLE 4

N-[2-Hydroxy-5-[1-hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenyl]methanesulphonamide

Intermediate 4 (0.98g) in absolute ethanol (20ml) was hydrogenated over 10% palladium on charcoal (50mg) and 5% platinum on charcoal (50mg) catalysts. The mixture was filtered through hyflo and evaporated *in vacuo*. The residual brown oil (0.72g) solidified on trituration with ER to afford the *title compound* (0.34g) m.p. 89-91°.

Found:	C,61.8;	H,7.7;	N,5.55.
$C_{25}H_{38}N_2O_5S.0.25H_2O$ requires	C,62.1;	H,8.0;	N,5.8%.

EXAMPLE 5

N-[2-Hydroxy-5-[1-hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenyl]urea

A solution of Intermediates 5 (0.7g) in ethanol (15ml) was hydrogenated over 10% palladium on charcoal (50mg) and 5% platinum on charcoal (50mg) catalysts. The mixture was filtered through hyflo and evaporated *in vacuo* to give a yellow oil which was triturated with ER to give an off-white solid (0.32g), m.p. 87-89°. T.l.c. (EA-ME 1:1) Rf 0.18.

EXAMPLE 6

N-[2-Hydroxy-5-[1-hydroxy-2-[[1-methyl-6-(2-phenylethoxy)hexyl]amino]ethyl]phenyl]methanesulphonamide

A solution of [7-[2-phenylethoxy]heptan-2-one (0.70g) and *N*-[5-[2-[bis(phenylmethyl)amino]-1-oxoethyl]-2-(phenylmethoxy)phenyl]methanesulphonamide (1.54g) in absolute ethanol (50mℓ) was hydrogenated over a mixture of pre-reduced 5% platinum on charcoal (250mg) and 10% palladium on charcoal (250mg) catalysts in ethanol (25mℓ). The mixture was filtered through hyflo and evaporated *in vacuo* to give a white solid (1.3g). Purification by [FCS] on triethylamine deactivated silica (Merck 9385, 50g) eluting with EA-ME (9:2) followed by trituration with ER gave the *title compound* as a white solid (0.88g) m.p. 122.5-123.5°.

Found:	C,60.3;	H,7.7;	N,5.9.
$C_{24}H_{36}N_2O_5S.0.75H_2O$ requires	C,60.3;	H,7.9;	N,5.9%.

EXAMPLE 7

N-[2-Hydroxy-5-[1-hydroxy-2-[[6-[4-(4-fluorophenyl)butoxy]hexyl]amino]ethyl]phenyl]methanesulphonamide

A solution of Intermediate 8 (0.25g) in absolute ethanol (10mℓ) was hydrogenated over a pre-reduced mixture of 10% palladium on charcoal (40mg) and 5% platinum on charcoal (40mg) catalysts in ethanol (5mℓ). The mixture was filtered through hyflo and evaporated *in vacuo* to give a brown oil which on trituration with ER gave the *title compound* as an off-white solid (0.15g) m.p. 84-85° (dec).

Found:	C,56.5;	H,7.4;	N,5.4.
$C_{25}H_{37}FN_2O_5S.2H_2O$ requires	C,56.4;	H,7.8;	N,5.3%.

EXAMPLE 8

N-[2-Hydroxy-5-[1-hydroxy-2-[[6-(3-phenylpropoxy)hexyl]amino]ethyl]phenyl]propanesulphonamide

A solution of Intermediate 11 (0.65g) in absolute ethanol (40mℓ) was hydrogenated over a mixture of pre-reduced 10% palladium on charcoal (150mg) and 5% platinum on charcoal (150mg) catalysts in ethanol (10mℓ). The mixture was filtered through hyflo and evaporated *in vacuo* to give a yellow oil which on trituration with ER gave the *title compound* as a white solid (170mg) m.p. 82-83.5° (dec).

Found:	C,62.3;	H,7.9;	N,5.5.
$C_{26}H_{40}N_2O_5S.0.5H_2O$ requires	C,62.2;	H,8.2;	N,5.6%.

EXAMPLE 9

N-[2-Hydroxy-5-[1-hydroxy-2-[[3-[(6-phenylhexyl)oxy]propyl]amino]ethyl]phenyl]methanesulphonamide, benzoate (salt)

Intermediate 15 (0.69g) in DMF (2mℓ) was added dropwise to a solution of *N*-[5-[(2-amino-1-hydroxyethyl)]-2-hydroxy-phenyl-methanesulphonamide (0.85g) and *N,N*-diisopropylethylamine (0.33g) in DMF (20mℓ) at 80° under nitrogen. The mixture was stirred at 80° for 3h, and evaporated *in vacuo*. The residual oil was dissolved in EA (50mℓ) and washed with water (100mℓ). The aqueous phase was re-extracted with EA (75mℓ), the combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil. Purification by [FCS] eluting with T-ET-A (39:10:1) gave a brown oil which was dissolved in ME (10mℓ) and treated with benzoic acid (0.08g). The solvent was evaporated *in vacuo* and the residue triturated with ER to give the *title compound* as an ivory solid (140mg) mp.p 133-133.5°.

Found:	C,62.79;	H,7.27;	N,4.77.
$C_{24}H_{36}N_2O_5S.0_7H_6O_2.0.5H_2O$ requires	C,62.50;	H7.28;	N,4.70%.

EXAMPLE 10

N-[2-Hydroxy-5-[1-hydroxy-2-[[5-(4-phenylbutoxy)penyl]amino]ethyl]phenyl]acetamide

A solution of *N*-[5-bromoacetyl-2-(phenylmethoxy)phenyl]acetamide (1.00g), Intermediate 17 (0.9g) and *N,N*-diisopropylethylamine (0.46g) in DMF (50mℓ) was stirred under nitrogen for 6h. The solution was diluted with water (50mℓ) and extracted with EA (2×100mℓ) and washed with 2N hydrochloride acid (50mℓ), 2N sodium bicarbonate (50mℓ), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil which crystallised on standing. The resulting cream solid (1.67g) was dissolved in ethanol (90mℓ) and hydrogenated over a mixture of pre-reduced 10% palladium oxide on charcoal (300mg) and 5% platinum oxide on charcoal (300mg) catalysts in ethanol (25mℓ). The mixture was filtered through hyflo and

evaporated *in vacuo* to give an oil which on trituration with ER gave a brown foam. Purification by [FRC] eluting with T-ET-A (39 : 10 : 1) gave an oil which on trituration with ER gave the *title compound* as a brown foam (0.31g). T.l.c. (T-ET-A 39 : 10 : 1) Rf 0.26.

Found:	C,68.66;	H,8.53;	N,6.39.	
$C_{25}H_{36}N_2O_4.0.5H_2O$ requires	C,68.62;	H,8.52;	N,6.40%.	

EXAMPLE 11

N'-[2-Hydroxy-5-[1-hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenyl]-N,N-dimethylsulphamide

A solution of Intermediate 16 (0.61g) in absolute ethanol (30mℓ) was hydrogenated over a mixture of pre-reduced 5% platinum oxide on charcoal (150mg) and 10% palladium oxide on charcoal (150mg) catalysts in ethanol (10mℓ). The mixture was filtered through hyflo and evaporated *in vacuo* to give an oil. Purification by [FCS] eluting with T-ET-A (39 : 10 : 1) gave a brown oil, which on trituration with ER gave a cream solid (0.20g), m.p. 75-77°.

Found:	C,60.96;	H,8.12;	N,8.16.	
$C_{26}H_{41}N_3O_3S$ requires	C,61;51;	H,8.14;	N,8.28%.	

EXAMPLE 12

N-[2-Hydroxy-5-[1-hydroxy-2-[[6-[4-(4-methylphenyl)butoxy]hexyl]amino]ethyl]phenyl]methanesulphonamide

A solution of N-[5-(bromoacetyl)-2-(phenylmethoxy)phenyl]methanesulphonamide (1.0g), the amine (0.9g) obtained by basification of Intermediate 13, and N,N-diisopropylethylamine (0.4g) in THF (20mℓ) was left at room temperature for 18h, filtered and evaporated. The residue was purified by [C] eluting with CX-ER (1:1) to give a yellow oil (1.0g). The oil in ethanol (50mℓ) and THF (30mℓ) was hydrogenated over 10% palladium on charcoal (0.4g) and 5% platinum on charcoal (0.3g) for 5h, filtered and evaporated. The residue was purified by [C] eluting with T-ET-A (80:20:1) to give a yellow gum, which was triturated with ER (40mℓ) to give the *title compound* as a yellow solid (0.2g) m.p. 65-67°. T.l.c. (T-ET-A 80:20:1) Rf 0.2.

EXAMPLE 13

N-[2-Hydroxy-5-[1-hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenyl]methanesulphonamide, acetate(salt)

A solution of N-[2-hydroxy-5-[1-hydroxy-2-[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenyl]methanesulphonamide (4.0g) in chloroform (50ml) was treated with acetic acid (0.8g) and the chloroform was evaporated. The residue was triturated with ER (50ml) to leave a yellow solid which was recrystallised from EA-ME to give the *title compound* as a white solid (3.7g), m.p. 121-123°.

Found:	C,59.3;	H,7.9;	N,5.1.	
$C_{25}H_{38}N_2O_5S.C_2H_4O_2.0.5H_2O$ requires	C,59.2;	H,7.85;	N,5.1%.	

The following are examples of suitable formulations of compounds of the invention. The term "active ingredient" is used herein to represent a compound of the invention and may be, for example, the compound of Example 4.

Tablets

These may be prepared by the normal methods such as wet granulation or direct compression.

A. Direct Compression

	mg/tablet
Active ingredient	2.0
Microcrystalline Cellulose USP	196.5
Magnesium Stearate BP	1.5
Compression weight	200.0

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using 7mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to microcrystalline cellulose or the compression weight and using punches to suit.

B. Wet Granulation

	mg/tablet
Active ingredient	2.0
Lactose BP	151.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium Stearate BP	1.5
Compression weight	200.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using 7mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

C. For buccal administration

	mg/tablet
Active ingredient	2.0
Lactose BP	94.8
Sucrose BP	86.7
Hydroxypropylmethylcellulose	15.0
Magnesium Stearate BP	1.5
Compression weight	200.0

The active ingredient is sieved through a suitable sieve and blended with the lactose, sucrose and hydroxypropylmethylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using suitable punches.

The tablets may be film coated with suitable film forming materials, such as hydroxypropylmethylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Capsules

	mg/capsule
Active ingredient	2.0
* Starch 1500	97.0
Magnesium Stearate BP	1.0
Fill weight	100.0

* A form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary the capsule size to suit.

Syrup

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup

	mg/5ml dose
Active ingredient	2.0
Sucrose BP	2750.0
Glycerine BP	500.0
Buffer	)
Flavour	) as required
Colour	)
Preservative	)
Purified Water BP to	5.0ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup produced is clarified by filtration.

B. Sucrose-Free

	mg/5ml dose
Active ingredient	2.0mg
Hydroxypropyl methylcellulose USP (viscosity type 4000)	22.5mg
Buffer	)
Flavour	)
Colour	) as required
Preservative	)
Sweetner	)
Purified Water BP to	5.0ml

The hydroxypropyl methylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

Metered Dose Pressurised Aerosol

A. Suspension Aerosol

	mg/metered dose	Per can
Active ingredient micronised	0.100	26.40mg
Oleic Acid BP	0.100	2.64mg
Trichlorofluoromethane BP	23.64	5.67g
Dichlorodifluoromethane BP	61.25	14.70

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The Oleic Acid is mixed with the Trichlorofluoromethane at a temperature of 10-15°C and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves delivering 85mg of suspension are crimped onto the cans and the Dichlorodifluoromethane is pressure filled into the cans through the valves.

B. Solution Aerosol

	mg/metered dose	Per can
Active ingredient	0.055	13.20mg
Ethanol BP	11.100	2.66g
Dichlorotetrafluoroethane BP	25.160	6.04g
Dichlorodifluoromethane BP	37.740	9.06g

Oleic acid BP, or a suitable surfactant e.g. Span 85 (sorbitan trioleate) may also be included.
The active ingredient is dissolved in the ethanol together with the oleic acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the trichlorofluoromethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the valves.

Suppositories

Active ingredient	2.0mg
* Witepsol H15 to	1.0g

* A proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient in molten Witepsol is prepared and filled, using suitable machinery, into 1g size suppository moulds.

Injection for Intravenous Administration

	mg/ml
Active ingredient	0.5mg
Sodium Chloride BP	as required
Water for Injection BP to	1.0ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively suitable buffer salts may be used.
The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

Inhalation Cartridges

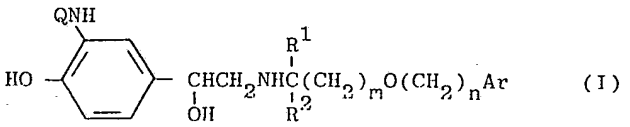
	mg/cartridge
Active ingredient micronised	0.200
Lactose BP to	25.0

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with

normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler such as the Glaxo Rotahaler.

CLAIMS

1. Compounds of the general formula (I)



(I)

wherein
m is an integer from 2 to 8 and
n is an integer from 1 to 7 with the proviso that the sum total of m+n is 4 to 12;
Ar represents a phenyl group optionally substituted by one or more substituents selected from halogen atoms,
C_{1-6} alkyl or C_{1-6} alkoxy groups, or an alkylenedioxy group of formula $-O(CH_2)_pO-$, where p represents 1 or 2;
R^1 and R^2 each represents a hydrogen atom or a C_{1-3} alkyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 4;
Q represents a group R^3CO-, R^3NHCO-, $R^3R^4NSO_2-$ or R^5SO_2- where R^3 and R^4 each represents a hydrogen atom or a C_{1-3} alkyl group and R^5 represents a C_{1-4} alkyl group; and physiologically acceptable salts and solvates thereof.

2. Compounds as claimed in claim 1, in which the total number of carbon atoms in the chains $-(CH_2)_m-$ and $-(CH_2)_n$ is 7 to 10 inclusive.

3. Compounds as claimed in claim 2, in which m is 2 or 3 and n is 6, or m is 4 and n is 3, 4 or 5, or m is 5 and n is 2, 3 or 4.

4. Compounds as claimed in claim 3, in which m is 5 and n is 4.

5. Compounds as claimed in any of claims 1 to 4 in which R^1 and R^2 independently represent a hydrogen atom or a methyl group.

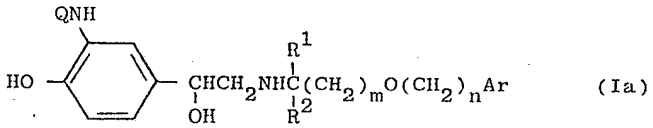
6. Compounds as claimed in claim 5 in which R^1 is a hydrogen atom and R^2 is a hydrogen atom or a methyl group.

7. Compounds as claimed in any of claims 1 to 6 in which Q is HCO−, CH_3CO-, NH_2CO-, $(CH_3)_2NSO_2-$, or R^5SO_2- where R^5 is C_{1-3} alkyl.

8. Compounds as claimed in claim 7 in which Q is R^5SO_2- where R^5 is methyl.

9. Compounds as claimed in any of claims 1 to 8 in which Ar is an unsubstituted phenyl group or is a phenyl group substituted by one substituent which is a methyl group or a fluorine atom.

10. Compounds of the general formula (Ia)



(Ia)

wherein m is an integer from 2 to 5, n is an integer from 2 to 6, and the sum total of m+n is 7, 8 or 9;
R^1 represents hydrogen and R^2 represents a hydrogen atom or a methyl group;
Ar represents a phenyl group optionally substituted by a methyl group or a fluorine atom; and
Q represents HCO−, CH_3CO-, NH_2CO-, $(CH_3)_2NSO_2-$ or R^5SO_2- where R^5 is C_{1-3} alkyl; and physiologically acceptable salts and solvates thereof.

11. Compounds of the general formula (Ia) according to claim 10 wherein m is 5 and n is 4, Q is CH_3SO_2-, and Ar is a phenyl group or a phenyl group substituted by a fluorine atom.

12. The compound:
N-[2-hydroxy-5-[1-hydroxy-2[[6-(4-phenylbutoxy)hexyl]amino]ethyl]phenyl]methanesulphonamide and physiologically acceptable salts and solvates thereof.

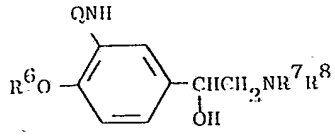
13. The compounds:
N-[2-hydroxy-5-[1-hydroxy-2-[[6-[4-(4-fluorophenyl)butoxy]hexyl]amino]ethyl]phenyl]methanesulphonamide;
N-[2-hydroxy-5-[1-hydroxy-2-[[1-methyl-6-(2-phenylethoxy)hexyl]amino]ethyl]phenyl]methansulphonamide;
N-[2-hydroxy-5-[1-hydroxy-2-[[6-(3-phenylpropoxy)hexyl]amino]ethyl]phenyl]formamide;
N-[2-hydroxy-5-[1-hydroxy-2-[[6-(4-phenyl-butoxy)hexyl]amino]ethyl]phenyl]urea;
N-[2-hydroxy-5-[1-hydroxy-2-[[3-[(6-phenylhexyl)oxy]propyl]amino]ethyl]phenyl]methanesulphonamide;
N-[2-hydroxy-5-[1-hydroxy-2-[[6-(3-phenylpropoxy)hexyl]amino]ethyl]phenyl]urea;

N-[2-hydroxy-5-[1-hydroxy-2-[[6-(3-phenylpropoxy)hexyl]amino]ethyl]phenyl]methanesulphonamide;
N-[2-hydroxy-5-[1-hydroxy-2-[[6-[4-(4-methylphenyl)butoxy]hexyl]amino]ethyl]phenyl]methanesulphonamide;
and physiologically acceptable salts and solvates thereof.

14. Compounds of formula (I) as defined in claim 1, in which m, n, R^1 and R^2 are as defined in claim 1, Ar represents a phenyl group optionally substituted by one or two substituents selected from halogen atoms, C_{1-3} alkyl or C_{1-3} alkoxy groups or an alkylenedioxy group of formula $-O(CH_2)_pO-$ where p is 1 or 2, and Q represents the group R^3CO , R^3NHCO- or R^3SO_2- where R^3 and R^4 are as defined in claim 1, and R^5 is C_{1-3} alkyl.

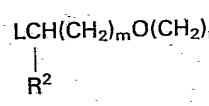
15. A process for the preparation of compounds as claimed in any of claims 1 to 14 or a physiologically acceptable salt or solvate thereof which comprises:

(1a) for the preparation of a compound of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (II)



(II)

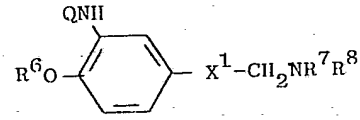
(where each of R^6 and R^7 is a hydrogen atom or a protecting group and R^8 is a hydrogen atom) with an alkylating agent of general formula (III)



(III)

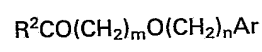
(wherein L represents a leaving group) followed, if necessary, by removal of any protecting group present; or

(1b) for the preparation of a compound of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (IV).



(IV)

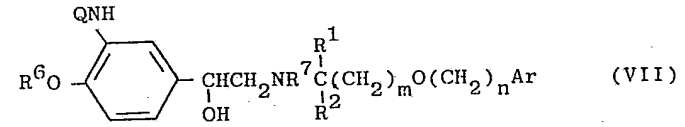
(where each of R^6 and R^7 is a hydrogen atom or a protecting group, R^8 represents a hydrogen atom or a group convertible thereto under the reaction conditions, and X^1 represents $-CH(OH)-$ or $>C=O$) with a compound of general formula (V)



(V)

in the presence of a reducing agent followed, if necessary, by removal of any protecting group present; or

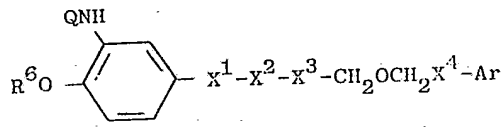
(2) deprotection of a protected intermediate of general formula (VII)



(VII)

(where each of R^6 and R^7 is a hydrogen atom or a protecting group, except that at least one of R^6 and R^7 is a protecting group); or

(3) reducing an intermediate of general formula (VIII)



(VIII)

(wherein R^6 is a hydrogen atom or a protecting group,
X^1 is $-CH(OH)$ or a group convertible thereto by reduction,
X^2 is $-CH_2NR^7$ or a group convertible thereto by reduction,
X^3 is $-CH^1R^2(CH_2)_{m-1}$ or a group convertible thereto by reduction, and
X^4 is $-(CH_2)_{n-1}$ or a group convertible thereto by reduction.
at least one of X^1, X^2, X^3 and X^4 representing a reducible group) followed, if necessary, by removal of any protecting group present; and

if desired, converting the resulting compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

16. A pharmaceutical composition comprising at least one compound of general formula (I) as defined in any of claims 1 to 14 or a physiologically acceptable salt or solvate thereof, together with a physiologically acceptable carrier or excipient.

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